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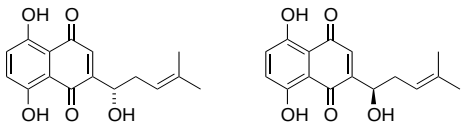
Concise and Efficient Total Syntheses of Alkannin and Shikonin**

K. C. Nicolaou* and David Hepworth

In ancient times extracts from the roots of *Alkanna tinctoria* in Europe and *Lithospermum erythrorhizon* in the Orient were used as natural purple dyes. More interestingly, Dioscorides recorded their use in ointments for the healing of wounds.[1] Early this century the enantiomeric naphthoquinones alkannin (**1**) and shikonin (**2**) (Scheme 1) were isolated[2] and identified[3] from these extracts. In fact, these natural products have been found in many species of Boraginaceae,[4] both as the free alcohols and ester derivatives—the ratio of enantiomers varies not only with species but also between the different derivatives.[5] More recently the wound-healing properties of these root extracts, which had drifted into folklore, were confirmed experimentally by Papageorgiou, and the active components identified as **1**, **2**, and closely related derivatives.[6] These natural products exhibit many other interesting biological effects including antibacterial,[7] antifungal,[8] anti-inflammatory,[9] antitumor,[10] analgesic,[9a,11] antipyretic,[12] and immunostimulatory[13] activities. In spite of the apparently simple molecular structures of **1** and **2**, short and efficient syntheses remained elusive. This, coupled with the extraordinary biological properties of these natural products, prompted us to investigate their total syntheses.

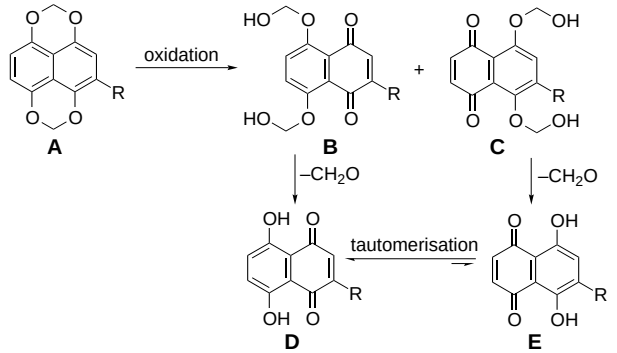


1 **2**

Scheme 1. Structures of alkannin (**1**) and shikonin (**2**).

Successful syntheses of **1** and **2** reported thus far have involved the use of 1,4,5,8-tetramethoxynaphthalene derivatives,[14] with only one exception.[15] While this protecting regime for the 5,8-dihydroxynaphthoquinone (naphthazarin) core has enabled the assembly of the side chain by several routes,[14] the final deprotection sequences to reveal the quinone system of the natural product are low-yielding and impractical. There are three major problems associated with the use of this protected system: a) initial oxidation using ceric ammonium nitrate (CAN) gives rise to two regioisomeric dimethoxynaphthoquinones with no or negligible selectivity.[14,16] Only one of these isomers can be converted into a naphthazarin in a single step;[14c,f,17] b) removal of the second pair of methyl protecting groups requires very harsh conditions ($Ag^{II}O$, HNO_3, dioxane) and gives only a poor yield of the naphthazarin derivative,[14a–f,18] and c) the drastic conditions for deprotection of the aromatic system make it prudent to protect the side-chain hydroxyl.[14e] The sensitivity of the natural products to acidic conditions[4a,14b] and to light and oxygen must also be addressed in designing efficient syntheses.[19]

We aimed to apply a novel protecting system for the naphthoquinone moiety, so that removal could be effected in one step (thus avoiding problems of regioselectivity of the oxidation) and under mild conditions compatible with an unprotected hydroxyl group. Furthermore, it was projected that this could be achieved through the use of the bismethyleneacetal derivatives of type **A** (Scheme 2). The isomers **D** and **E** should rapidly tautomerize in favor of the



A **B** **C** **D** **E**

Scheme 2. Strategy for the selective generation of **1** and **2** from bismethyleneacetal derivatives.

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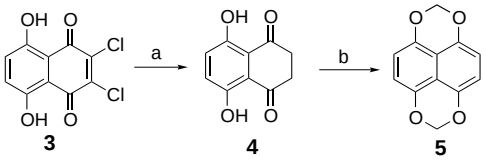
desired form **D**, by virtue of the stabilizing effect of the electron-donating alkyl group (Scheme 2).[20]

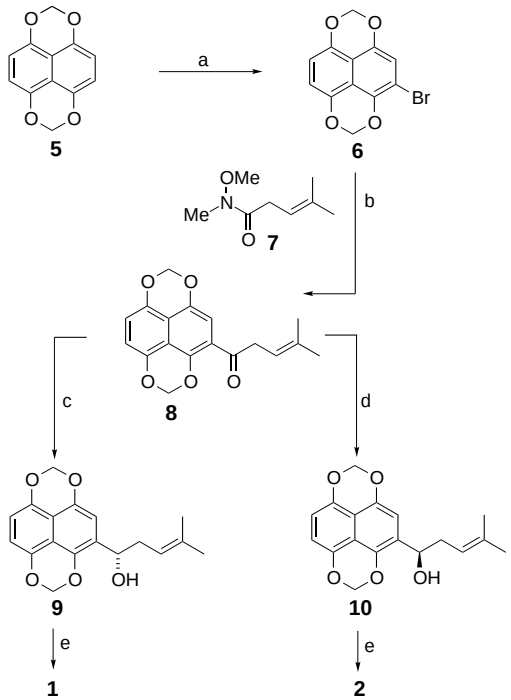
As 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin) itself is prohibitively expensive, we expected that the more efficiently synthesized 2,3-dichloronaphthazarin (**3**) would provide us with a more viable source for the naphthoquinone core, since it can be readily produced in large quantities by Friedel–Crafts acylation.[21] Furthermore, we anticipated that an asymmetric ketone reduction would be an effective way of producing both enantiomers from a common late-stage intermediate. Thus, treatment of **3** with $SnCl_2$ in 4 M HCl at reflux causes reduction of the quinone with concomitant dechlorination to afford leuconaphthazarin (**4**) as its moderately air-sensitive diketo tautomer (Scheme 3).[22] Methyleneacetal formation according to the literature procedure provides intermediate **5** in good yield.[23]



Scheme 3. Synthesis of **5**: a) $SnCl_2$, 4 M HCl, reflux, 5 h, 90%; b) $BrClCH_2$, K_2CO_3, DMF, 100°C, 18 h, 70%. DMF = *N*,*N*-dimethylformamide.

Monobromination of **5** was achieved by treatment with *N*-bromosuccinimide (NBS) in $CHCl_3$ to afford **6** (70%) (Scheme 4). Halogen–metal exchange at low temperature using *t*BuLi followed by addition of the Weinreb amide **7**,[24] synthesized from the known carboxylic acid precursor by a standard procedure in 61% yield,[25] afforded ketone **8** as a yellow crystalline solid (63% plus 23% recovered **5**; Table 1). Asymmetric reduction of **8** was found to be most effective with diisopinocampheylchloroborane (DIP-Cl),[26] which provided enantiomeric alcohols **9** [with (+)-DIP-Cl] and **10** [with (−)-DIP-Cl] in excellent enantiomeric excesses ($\geq$98%)[27] and high yields (93%).

Attempts to reveal the naphthoquinone core from the methyleneacetal-protected system by using chemical oxidants (e.g. CAN, $Ag^{II}O$, MnO_2) gave disappointing results and required protection of the side-chain hydroxyl. However, mild anodic oxidation of the free hydroxy derivatives **9** and **10** avoided an undesirable protection–deprotection sequence. As envisioned, the one-step deprotection procedure allowed easy and relatively efficient access to each naturally occurring enantiomer, alkannin (**1**) and shikonin (**2**) (80% yield at ca. 50% conversion). Analytical data were consistent with those previously reported for the natural products (^{1}H NMR,[14,28] ^{13}C NMR,[14,28] IR,[14] UV,[3] HRMS,[14a,b] CD,[5a,14e] m.p.;[3] Table 1). Furthermore, the anodic oxidation was performed with a simple experimental set-up: an undivided cell with graphite electrodes, a constant external voltage across the cell (3 V),[29] 50% aqueous acetonitrile as solvent, and 1 M $LiClO_4$ as electrolyte. At less than 50% conversion, TLC analysis showed clean conversion to the desired product. Side products only began to appear as the reaction proceeded to higher



Scheme 4. Total synthesis of alkannin (**1**) and shikonin (**2**): a) NBS (1 equiv), $CHCl_3$, 25°C, 12 h, 70%; b) *t*BuLi (2 equiv), THF, −78°C, 1 h, then **7**, −78°C, 1.5 h, 63% (23% recovered **5**); c) (+)-DIP-Cl (1.5 equiv), THF, −40°C → −25°C, 3 h, then CH_3CHO (2 equiv), 0°C, 12 h, 93%, $\geq$98% *ee*; d) (−)-DIP-Cl (1.5 equiv), THF, −40°C → −25°C, 3 h, then CH_3CHO (2 equiv), 0°C, 12 h, 93%, $\geq$98% *ee*; e) anodic oxidation, CH_3CN/H_2O (1:1), $LiClO_4$ (1M), graphite electrodes, undivided cell, 3 V constant external voltage, 25°C, 80% at ca. 50% conversion.

Table 1. Selected physical properties of compounds **8**–**10**, **1**, and **2**.

8: R_f = 0.49; (silica gel, 10% Et_2O in hexanes); m.p. 110–117°C (decomp); IR (KBr): $\tilde{\nu}_{max}$ = 3072, 2966, 2911, 1666, 1622, 1598, 1480, 1425, 1378, 1251, 1218, 1169, 1049, 969 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (s, 1H; C^5-H), 6.98, 6.92 (AB, J = 8.3 Hz, 1H; C^6-H, C^7-H), 5.62 (s, 2H; CH_2O), 5.51 (s, 2H; CH_2O), 5.47 (tq, J = 6.9, 1.3 Hz, 1H; CH=C), 3.82 (d, J = 6.9 Hz, 2H; CH_2C=O), 1.77 (d, J = 1.0 Hz, 3H; *trans* CH_3), 1.68 (s, 3H; *cis* CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 197.1, 145.8, 145.6, 144.6, 144.1, 135.4, 119.3, 117.1, 116.3, 115.0, 111.8, 110.1, 107.7, 91.7, 91.4, 43.5, 25.9, 18.3; HR-MS (fast atom bombardment; FAB) calcd for $C_{18}H_{17}O_5$ [M+H$^+$]: 313.1076; found: 313.1065.

9: R_f = 0.27 (silica gel, 33% Et_2O in hexanes); $[\alpha]_D^{22}$ = +80.2 (c = 1.48, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3397, 2914, 1614, 1477, 1418, 1380, 1250, 1162, 1047, 1011, 973, 879, 823 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.02 (s, 1H; C^3-H), 6.80, 6.77 (AB, J = 8.3, 1H; C^6-H, C^7-H), 5.51 (d, J = 5.0 Hz, 1H; CH_2O), 5.50 (d, J = 4.4 Hz, 1H; CH_2O), 5.46 (d, J = 5.2 Hz, 1H; CH_2O), 5.45 (d, J = 5.1 Hz, 1H; CH_2O), 5.19 (dt, J = 6.8, 1.2 Hz, 1H; CH=C), 5.13 (dd, J = 7.7, 5.5 Hz, 1H; C*H*OH), 2.53–2.42 (m, 3H; CH_2CHO*H*), 1.71 (s, 3H; CH_3), 1.61 (s, 3H; CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 144.4, 144.3, 144.3, 140.3, 135.7, 125.2, 119.4, 114.8, 114.3, 108.8, 108.2, 106.8, 91.7, 91.5, 67.7, 67.7, 36.8, 25.8, 17.9; HR-MS (FAB) calcd for $C_{18}H_{19}O_5$: [M^+] 314.1154, found: 314.1144.

10: as for **9** except $[\alpha]_D^{22}$ = −80.2 (c = 1.26, $CHCl_3$).

1 and **2**: R_f = 0.55 [silica gel (prewashed with 10% AcOH in CH_2Cl_2), 33% Et_2O in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.60 (s, 1H; $C^{5/8}$-H), 12.50 (s, 1H; $C^{5/8}$-H), 7.20, 7.18 (AB, J = 9.6, 1H; C^6-H, C^7-H), 7.17 (d, J = 1.2 Hz, 1H; C^3H), 5.20 (dt, J = 6.8, 1.3 Hz, 1H; CH=C), 4.92 (ddd, J = 7.9, 4.3, 1.0 Hz, 1H; C*H*OH), 2.68–2.62 (m, 1H; CH_2), 2.39–2.32 (m, 2H; CH_2CHO*H*), 1.76 (s, 3H; CH_3), 1.66 (s, 3H; CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 180.6, 179.8, 165.5, 164.9, 151.4, 137.4, 132.4, 132.3, 131.8, 118.4, 112.0, 111.5, 68.4, 68.3, 35.7, 25.9, 18.1.

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conversion. We anticipate that the efficiency of this step may be further improved by employing more sophisticated electrochemical equipment, in particular, through precise voltage control.

In conclusion, we have developed a novel protecting system for 5,8-dihydroxynaphthoquinones, which may be removed easily under mild conditions. This development, together with a highly enantioselective ketone reduction, has allowed us to complete concise and practical syntheses of each of the enantiomers alkannin (**1**) and shikonin (**2**). Chemical synthesis and biological investigations of a series of structural analogues of the natural products, more diverse than simple ester derivatives, are now viable. Further studies into the chemical biology of these compounds are in progress.

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A Naphthalene-Like Si_{10}^{10-} Unit in the Novel $^2_\infty[Si_{20}^{30-}]$ Planar Anion of $Sr_{13}Mg_2Si_{20}$**

Antonio Currao and Reinhard Nesper*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

In recent years, a large number of novel silicon Zintl anions[1] in the ternary and quaternary solids $M^1M^2Si_x$ and $M^1M^2M^3Si_x$ ($M^1 - M^3$ = alkali or alkaline earth metal) have been discovered and characterized.[2–5] Unequivocal evidence for a structure-directing influence of the metal atom on its respective Zintl anion Si_m^{n-} was observed relatively early; this effect may be exploited as a strategic aid in synthesis.[3] As was established for the oligomeric Si_m^{n-} polyanions, small, strongly polarizing cations (especially Mg^{2+}) coordinate formally highly charged terminal or isolated Si^{n-} anions, whereas larger, weakly charged cations are in the more highly networked regions of the polyanion.[2, 4] This phenomenon was used to tune the relative ratio of terminal to more highly networked atoms, the latter embedded deeper in the anion, while maintaining an identical valence electron count and mean bond order within the polyanion. In other words, the degree of disproportionation of the Si_x units is a function of the various cations and their respective stoichiometries. An unusual number of planar Si_m^{n-} polyanions have been reported

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